

U.S. Serial No.: 09/174,937

-2-

Group Art Unit: 1653

In the Specification:

Please replace lines 3-10 at page 10 with:

--In another embodiment, a NIP2b, NIP2cL, and NIP2cS of the present invention is identified based on the presence of a "calcium-binding domain" in the protein or corresponding nucleic acid molecule. As used herein, the term "calcium-binding domain" includes a protein domain having an amino acid sequence of about 110 amino acids which has the capacity to bind calcium. Preferably, a calcium binding domain includes a protein domain which is at least 50, 60, 70, 80, 90, or 100 amino acid residues in length and which has the capacity to bind calcium. The calcium-binding domain HMM has been assigned the PFAM Accession MILPAT0063 (Bateman, A., *et al.* (2000) NAR 28: 263-266). --

Please replace lines 11-28 at page 10 with:

--To identify the presence of a calcium-binding domain in a NIP2b, NIP2cL, or NIP2cS protein, and make the determination that a protein of interest has a particular profile, the amino acid sequence of the protein is searched against a database of HMMs (e.g., the Pfam database, release 2.1) using the default parameters (Bateman, A., *et al.* (2000) NAR 28: 263-266). For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default program for MILPAT0063 and a score of 15 is the default threshold score for determining a hit. Alternatively, the threshold score for determining a hit can be lowered (e.g., to 8 bits). A description of the Pfam database can be found in Sonhammer *et al.* (1997) *Proteins* 28(3):405-420 and a detailed description of HMMs can be found, for example, in Gribskov *et al.* (1990) *Meth. Enzymol.* 183:146-159; Gribskov *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:4355-4358; Krogh *et al.* (1994) *J. Mol. Biol.* 235:1501-1531; and Stultz *et al.* (1993) *Protein Sci.* 2:305-314, the contents of which are incorporated herein by reference. A search was performed against the HMM database resulting in the identification of a calcium-binding domain in the amino acid sequence of NIP2cL (SEQ ID NO: 5) at about residues 55-160 of SEQ

U.S. Serial No.: 09/174,937

-3-

Group Art Unit: 1653

ID NO:5 and NIP2cS (SEQ ID NO:8) at about residues 59-96 of SEQ ID NO:8. The results of the searches are set forth in Figures 8 and 9, respectively.—

Please replace the paragraph beginning at page 10, line 33 and ending at page 11, line 11 with:

--In another embodiment, a NIP2b, NIP2cL, and NIP2cS of the present invention is identified based on the presence of a "4 transmembrane segment integral membrane protein domain" in the protein or corresponding nucleic acid molecule. As used herein, the term "4 transmembrane segment integral membrane protein domain" includes a protein domain having an amino acid sequence of about 50 amino acid residues and having a bit score for the alignment of the sequence to the "4 transmembrane segment integral membrane protein domain" (HMM) of at least 1 or greater. Preferably the term "4 transmembrane segment integral membrane protein domain" includes a protein domain having an amino acid sequence of about 60, 70, 80, or 90 amino acids and having a bit score for the alignment of the sequence to the "4 transmembrane segment integral membrane protein domain" (HMM) of at least 2, preferably 3-10, more preferably 10-30, more preferably 30-50, even more preferably 50-75, 75-100, 100-200 or greater. The "4 transmembrane segment integral membrane protein domain" HMM has been assigned the PFAM Accession PF00335 (Bateman, A., *et al* (2000) NAR 28: 263-266). A search was performed against the HMM database, as described herein, resulting in the identification of a "4 transmembrane segment integral membrane protein domain" in the amino acid sequence of NIP2b (SEQ ID NO:2) at about residues 253 to 293. The results of the search are set forth in Figure 7.--

Please replace lines 22-35 at page 28 with:

--The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available from Accelrys, Inc., San Diego, CA), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent

U.S. Serial No.: 09/174,937

-4-

Group Art Unit: 1653

identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available from Accelrys, Inc., San Diego, CA), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. --

Please replace the paragraph beginning at page 28, line 34 and ending at page 29, line 8 with:

--The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to NIP2b, NIP2cL, and NIP2cS nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to NIP2b, NIP2cL, and NIP2cS protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used (Altschul, S.F., *et al.* (1990) *J. Mol. Biol.* 215:403-410; Altschul, S.F., *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402).--

#### **Remarks**

Applicants and their attorney thank the Examiner for the courtesy of the May 9, 2002 telephonic interview during which the Examiner indicated that Applicants' arguments (presented in the Amendment and Response to Final Office Action dated October 18, 2001) were sufficient to overcome the outstanding rejections under 35 U.S.C. §101 and §112.